

REMARKS

The Office Action of December 30, 2005, and the prior art applied therein, including the newly cited prior art, have been carefully studied. The claims in the application are now claims 1 and 5-20, and these claims define novel and unobvious subject matter under Sections 102 and 103, and therefore should be allowed. Applicants accordingly respectfully solicit favorable reconsideration and allowance.

New claim 20 has been added which is similar to claim 1, except that it employs a means clause under the provisions of 35 U.S.C. 112. New claim 20 is patentable for the same reasons as the other claims, as pointed out below.

Claims 1, 5-11 and 17-19 have been rejected as obvious under section 103 from Cahen in view of newly cited Harvey et al USP 5,945,832 ("Harvey"). This rejection is respectfully traversed.

Regarding claim 1, the rejection states: "Cahen et al. disclose a hybrid organic-semiconductor device characterized by being composed of: (i) at least one layer of a conducting semiconductor; (ii) at least one insulating layer; (iii) a multifunctional organic sensing molecule directly chemisorbed on one of its surfaces, said

multifunctional organic sensing molecule having at least one functional group that binds to said surface and at least one other functional group that serves as a sensor; and (iv) two conducting pads on the top layer making electrical contact with the electrically conducting layer, such that electrical current can flow between them at a finite distance from the surface of the device. In addition, Cahen et al. disclose a semiconductor device wherein: said conducting semiconductor layer is on top of one of said insulating or semi-insulating layers, said two conducting pads are on both sides on top of an upper layer which is either said conducting semiconductor layer or another of said insulating or semi-insulating layers, making electrical contact with said conducting semiconductor layer (Fig 2A, 2B). Cahen et al. do not disclose a layer of single-stranded DNA or RNA directly adsorbed to an upper layer which is either said conducting semiconductor layer or another of said insulating or semi-insulating layers wherein exposure of single-stranded DNA probe to a sample containing a target DNA or RNA, under hybridization conditions, causes either a current change resulting from the hybridization process when a constant electric potential is applied between the two conducting pads or a change in the electric potential required to keep a constant current".

The rejection further states that "Harvey et al. disclose a semi-conductor device (Figs. 1-3, for example) used in a method for the measurement of electrical characteristics of organic molecules (Col. 2, Lines 1-10; Col. 3, Lines 10-40, for example). They further disclose layers of single-stranded DNA (Column 3, lines 10-15, for example) bridging the gap between electrical contacts (Figs. 1-3, for example). Moreover, they specifically disclose that hybridization can be detected by a change in the electrical characteristics brought on by duplex formation (Col. 3, Lines 35-40)".

Thus, according to the rejection, "based on the combined disclosures of the applied references, one of ordinary skill in the art at the time of invention would have had a reasonable expectation of success directly adsorbing a layer of single-stranded DNA or RNA to the semi-conductor device of Cahen et al., wherein exposure of said single-stranded DNA probe to a sample containing a target DNA or RNA, under hybridization conditions, causes either a current change resulting from the hybridization process when a constant electric potential is applied between the two conducting pads or a change in the electric potential required to keep a constant current. The motivation to do so, provided by Harvey et al., would have been to detect DNA hybridization. At the time of the invention, the disclosure of Harvey et al. clearly

would have provided the instruction necessary for one of ordinary skill in the art at the time of invention to practice the instant methods as claimed". Applicants respectfully disagree for the following reasons.

Harvey discloses a device for measuring electrical characteristics of an organic molecule, comprising a first metal contact having a major surface; an insulating layer overlaying the major surface of the first metal contact; and a second metal contact overlaying the insulating layer and having an edge spaced a molecular distance from the major surface of the first metal contact. A conductive organic molecule including a metal binding group at each end is coupled between the metal contacts, forming a bridge therebetween, and the measured electrical characteristics of the bridge provides information about the electrical properties of the bridging molecule. The device of Harvey could be applied to study conductive molecules or detect the hybridization of DNA, wherein a single-stranded DNA bridging the gap between the two electrical contacts will have specific electrical properties, whereas hybridization of said single-stranded DNA into a double-stranded DNA can be detected by a change in the electrical characteristics brought on by duplex formation (Col. 1, Line 47 to Col. 2, Line 7; Col. 3, Lines 7-38).

Although the device of Harvey is not a DNA electrochemical sensor such as the device of the formerly cited and applied Hashimoto, it appears that the principle of operation in both cases is very similar, even substantially the same, namely electric current flows through the DNA molecules which are directly bound to the electrodes. Contrary to this principle of operation, in the electronic DNA sensor of the instant application, the electric current flows through the semiconductor substrate while there is no charge transport by the DNA. The hybridization of the DNA directly adsorbed on the substrate causes a change of the electronic properties of the substrate resulting in a change in the current flowing through the substrate, which was unpredictable, thus surprising and non-obvious.

Accordingly, applicants' remarks from the preceding Reply raised against the proposed combination of Harvey in view Hashimoto apply equally or substantially equally to the present rejection, at least in part, and therefore such remarks from the preceding Reply are respectfully repeated by reference.

Neither Cahen nor Harvey give any hint of the principle of operation of the electronic DNA sensor of the present invention, wherein the electric current flows through the semi-conductor substrate while there is no charge

transport by the DNA. It therefore follows that no possible combination of Harvey and Cahen, or any modification of Cahen by something taken from Harvey, could lead to the claimed subject matter, even if such a combination were obvious. Applicants' independent claim 1, as well as new claim 20, defines non-obvious subject matter over the applied prior art.

Withdrawal of the rejection is in order and is respectfully requested.

Claim 19 has been included in the rejection even though it depends from and incorporates the subject matter of claim 14, which is not included in the rejection. Applicants therefore believe that as claim 19 includes the subject matter of claim 14, it (claim 19) was incorrectly included in the above rejection. Regardless, applicants remarks as made above apply to claim 19 even if claim 29 is interpreted as an independent claim.

In general, the claims which depend from independent claim 1, either directly or indirectly, incorporate the subject matter thereof, and therefore are patentable for the reasons pointed out above. This does not mean that applicants agree with the statements in the rejection concerning the dependent portions of the subsidiary claims. Applicants accordingly respectfully reserve the right to address the

dependent portions of the subsidiary claims in the future, if it should become necessary or desirable to do so.

Claims 12-16 have been rejected as obvious under Section 103 from Cahen in view of Harvey and further in view of newly cited and applied Chee et al USP 5,837,832 (Chee). This rejection is respectfully traversed.

According to the rejection, neither Cahen nor Harvey specifically disclose multiple single-stranded DNA probes comprising a sequence complementary to a mutation sequence of a gene responsible for a genetic disease or disorder. However, Chee is said to disclose DNA chips for detecting mutations comprising multiple single-stranded DNA probes comprising a sequence complementary to a mutation sequence of a gene responsible for a genetic disease or disorder (Fig. 2; Column 2, Lines 40-65, Columns 7-13, for example), and to further disclose several advantages of the probe arrays including the highly informative nature of each position on the array (Col. 14, Lines 1-15, for example).

The rejection states that, "based on the combined disclosures of the applied references, one of ordinary skill in the art... would have had a reasonable expectation of success practicing DNA hybridization detection techniques of Cahen et al. and Harvey et al. further comprising multiple single-stranded DNA probe arrays comprising a sequence

complementary to a mutation sequence of a gene responsible for a genetic disease or disorder... the disclosure of Chee et al. clearly would have provided the instruction necessary... to practice the method as claimed. It would have been *prima facie* obvious... to practice the instant methods as claimed".

Chee discloses a DNA chip containing array of oligonucleotide probes comprising probes complementary to the reference sequence as well as probes that differ by one or more bases from the complementary probes, that can be used to determine whether a target nucleic acid has a nucleotide sequence identical to or different from a specific reference sequence.

Accordingly, Chee does not make up for the deficiencies of the basic proposed combination of Cahen in view of Harvey, and indeed has not been cited for that purpose. Therefore, even if it were somehow obvious to modify Cahen in view of Chee, respectfully not admitted by applicants, the subject matter of applicants' claim would still not be reached. In short, applicants' remarks presented above in reply to the rejection based on Cahen in view of Harvey apply equally here, and are therefore respectfully repeated by reference.

Withdrawal of the rejection is in order and is respectfully requested.

Claims 1 and 5-19 have been rejected as obvious under Section 103 from Cahen in view of the 2002 publication of Connolly, 2002/0022223, hereinafter "Connolly".¹ This rejection is respectfully traversed.

Applicants first note that the Connolly publication is based on an application filed on April 7, 2000, which is after applicants' priority date of June 7, 1999. Applicants also note that the Connolly application is based on a non-provisional application filed April 7, 1999, but applicants do not know whether or not that provisional application supports the subject matter in the Connolly publication which is relied upon the rejection. However, even if Connolly is available as "prior art", applicants' claims still define non-obvious subject matter.

According to the rejection regarding claim 1, Connolly discloses a semi-conductor device used in a method for testing for the presence of a target nucleic acid molecule, and further discloses that the Connolly invention has the advantage of being used for multiple samples. Connolly further discloses layers of single-stranded DNA, and specifically discloses that a current between the two leads is indicative of the presence of the target nucleic acid.

¹ Applicants do not see that Connolly has been cited of record in the present application.

Based thereon, while referring to the combined disclosures of Cahen and Connolly, with the added advantage of using the device of Connolly for the detection of multiple samples, the PTO has raised the same arguments previously presented referring to the combined disclosures of Cahen and Harvey, concluding that "it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to practice the instant methods as claimed."

Connolly provides "a device for detecting the presence of a target nucleic acid molecule. The device has two electronic leads, where the ends of the leads are located near each other but are not in contact. One or more sets of two oligonucleotide probes are attached to the electronic leads. The oligonucleotide probes are positioned such that they cannot come into contact with one another and such that a target nucleic acid molecule, which has two sequences complementary to the probes can bind to both probes concurrently. A sample which may have the target nucleic acid molecule is contacted with the probes under selective hybridization conditions. If the target is present it bridges the gap between the probes. The target nucleic acid molecule may then carry current between the probes, or be used as a support to form a conductive wire between the two probes" (page 1 [0003, 0004], for example). Accordingly, it is clear

that in the device of Connolly, as it is in the device of Harvey, electric current flows through the oligonucleotide molecules attached to the electronic leads as well as through the target nucleic acid molecule. As applicants have already clarified, contrary to this principle of operation, in the electronic DNA sensor of the instant application the electric current flows through the semiconductor substrate while there is no charge transport by the DNA.

Consequently, Connolly being not unlike Harvey as regards the deficiencies discussed above with respect to the rejection based on Cahen in view of Harvey, applicants respectfully repeat by reference the remarks made above in reply to the rejection based on Cahen in view of Harvey. Thus, even if the references were obviously combinable, contrary to applicants' position, the resultant combination could not reach the claimed subject matter.

Applicants' claims define non-obvious subject matter over Cahen in view of Connolly. Withdrawal of the rejection is in order and is respectfully requested.

With respect to the rejected subsidiary claims, these all depend from and thus incorporate the subject matter of claim 1, either directly or indirectly. For that reason alone, all of the subsidiary claims also define non-obvious subject matter over any possible combination of Cahen in view

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of Connolly. Applicants respectfully reserve the right to address the dependent portions of the subsidiary claims at a later date, if it should become desirable or necessary to do so.

Withdrawal of the rejection of the subsidiary claims is respectfully requested.

The prior art documents of record and not relied upon by the PTO have been noted, along with the implication that such documents are deemed by the PTO to be insufficiently material to warrant their application against any of applicants' claims.

Applicant believes that all issues raised in the Office Action have been addressed above in a manner favorable to allowance of the present application. Accordingly, applicant respectfully requests favorable reconsideration and early formal allowance.

Respectfully submitted,

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